PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 12184611/RMH	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU2003/001446**	International Filing Date *(day/month/year)* 3 November 2003	Priority Date *(day/month/year)* 1 November 2002
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] C07D 311/68, A61K 31/352, A61P 35/00		
Applicant NOVOGEN RESEARCH PTY LTD et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand 31 May 2004	Date of completion of the report 21 February 2005
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **SWARUP CHATTERJEE** Telephone No. (02) 6283 2259

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001446

I. Basis of the report

1. With regard to the **elements** of the international application:*

- [ ] the international application as originally filed.
- [X] the description, pages **1-44**, as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [X] the claims, pages **45**, as originally filed,
  pages , as amended (together with any statement) under Article 19,
  pages , filed with the demand,
  pages **46, 48-55**, received on **31 January 2005** with the letter of **31 January 2005**
  47, received on **24 February 2005** with the letter of **24 February 2005**
- [X] the drawings, pages **1/7 – 7/7**, as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [ ] the sequence listing part of the description:
  pages , as originally filed
  pages , filed with the demand
  pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- [ ] contained in the international application in written form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form.
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages
   - [ ] the claims, Nos.
   - [ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **1-18**	**YES**
	Claims	**NO**
Inventive step (IS)	Claims **1-18**	**YES**
	Claims	**NO**
Industrial applicability (IA)	Claims **1-18**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

The International Search Report cited the following documents:

D1: WO 1992/018462

D2: WO 1990/007495

D3: Chemical Abstract Accession No 128:114885

D4: Chemical Abstract Accession No 124:250291

D5: Chemical Abstract Accession No 85:21030

D6: Chemical Abstract Accession No 77:19487

D7: Chemical Abstract Accession No 70:11493

D8: Chemical Abstract Accession No 70:4085

D9: Chemical Abstract Accession No 65:82115

D10: Chemical Abstract Accession No 58:33237

D11: Chemical Abstract Accession No 58:33236

D12: Chemical Abstract Accession No 55:118498

D13: Chemical Abstract Accession No 54:86477

As a result of the provisos included by the applicant in the letter of 31 January 2005 and 24 February 2005, claims 1-18 can be regarded as novel and inventive. The provisos have resulted in the exclusion of the following compounds:

D1 discloses compounds with RN 145961-44-0, 14961-52-0 and 145962-20-5; D4 discloses compounds with RN 175357-71-8 and 175357-72-9 (both relevant to claims 1, 7, 8, 11, 13, 15 and 16);

D5 disclose compounds with RN 59564-27-1 and 59564-28-2, prepared by the treatment of isoflavone with HONH2 (relevant to claims 1 and 6);

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

D2 disclose compounds with RN 131210-14-5, 131210-15-6, 131210-16-7, 131210-17-8, 131210-18-9, 131210-19-0, 131210-20-3, 131210-21-4 and 131210-22-5 (relevant to claim 1);

D3 discloses compounds with RN 201678-42-4 and 201678-41-3 (relevant to claim 1);

D6 discloses the compound with RN 36944-54-4 (relevant to claim 1);

D7 discloses compounds with RN 20986-74-7, 20986-75-8, 20986-76-9, 20986-79-2, 20986-80-5, 20986-81-6 and 23624-08-0 (relevant to claim 1);

D8 discloses compounds with RN 20991-23-5, 20991-24-6 and 20991-25-7 (relevant to claim 1);

D9 discloses the compound with RN 7622-46-0 (relevant to claim 1);

D10 discloses compounds with RN 97497-17-1, 100322-08-5, 100435-21-0 and 100767-92-8 (relevant to claim 1);

D11 discloses compounds with RN 59564-27-1, 89286-01-1, 89286-02-2, 89286-03-3, 97724-24-8, 100322-08-5, 100657-54-3, 100733-86-6, 100733-87-7, 100767-92-8 and 100802-67-3 (relevant to claim 1);

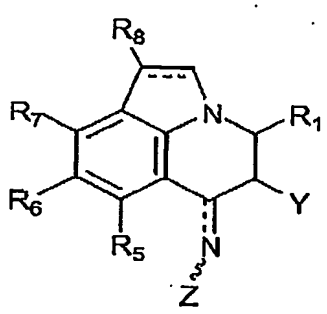
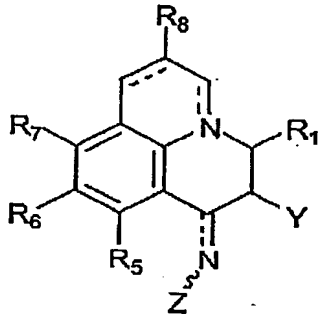
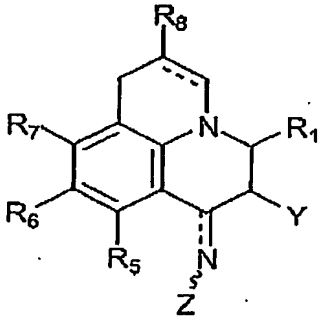
D12 discloses the compound with RN 122701-70-6 (relevant to claim 1);

D13 discloses compounds with RN 114863-28-4 and 114863-29-5 (relevant to claim 1).

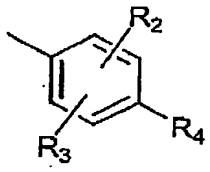
Claims 9, 10, 12, 14, 17 and 18 are novel and inventive when compared to D1-D13 because there is no disclosure of the methods, agents, compositions or drink/foodstuff of these claims, nor is there any disclosure that would render these obvious.

Claims 1-18 meet the requirement of industrial applicability.

or when X is NR_{12}, the substituent R_{12} may be a bond such that R_8 and X together with the carbon atoms to which they are attached form one of the following structures:

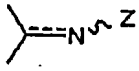
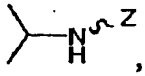




where Y is



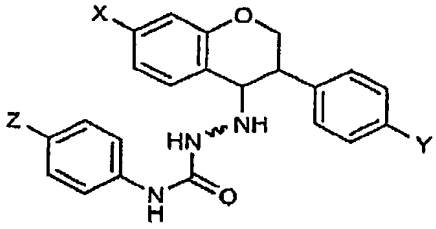
and wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and Z are as defined above, and

the drawing "---" represents either a single bond or a double bond and when it is a single bond, the drawing  represents  ,

which compounds include pharmaceutically acceptable salts and derivatives thereof

with the proviso that compounds of the formula

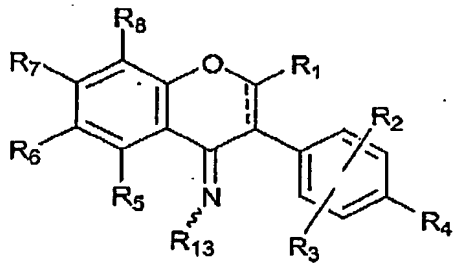


wherein

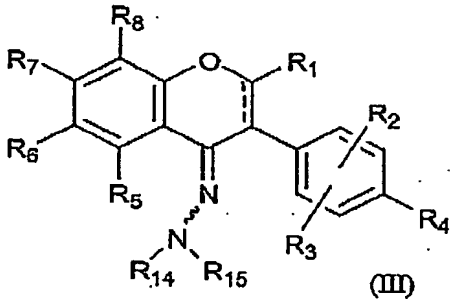
X is F or Cl,

7-Methoxy-isoflavanone (2,4-dinitrophenyl)hydrazone
7-Hydroxy-4'-methoxy-isoflavanone (2,4-dinitrophenyl)hydrazone
5,7-Dimethoxy-isoflavanone (2,4-dinitrophenyl)hydrazone
6-Methoxy-isoflavanone (2,4-dinitrophenyl)hydrazone
4',5,7-trimethoxy-isoflavanone (2,4-dinitrophenyl)hydrazone
7-Methoxy-2-methyl-isoflavanone (2,4-dinitrophenyl)hydrazone
2-(Hydroxymethyl)-7-methoxy-isoflavanone (2,4-dinitrophenyl)hydrazone
and hydrochloride salts thereof are specifically excluded.

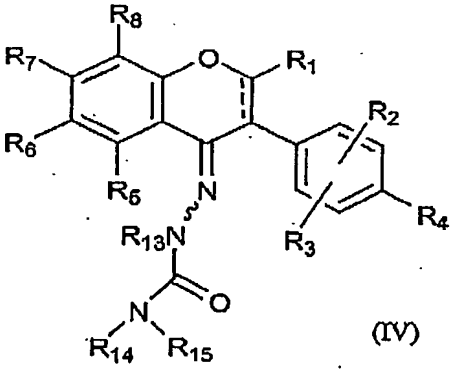
2. A compound according to claim 1, depicted by one of the general formulae (II)-(VIII):



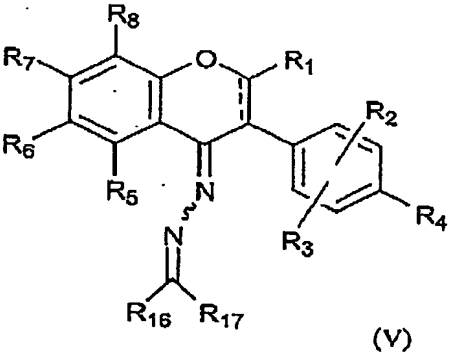
(II)



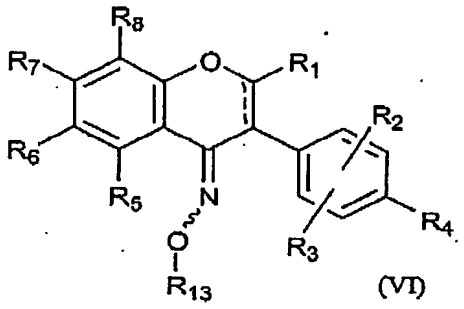
(III)



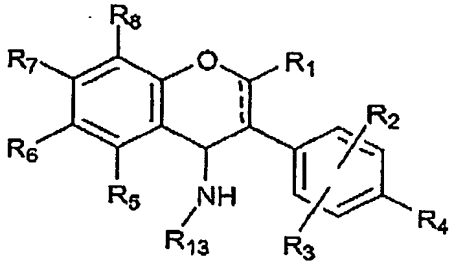
(IV)



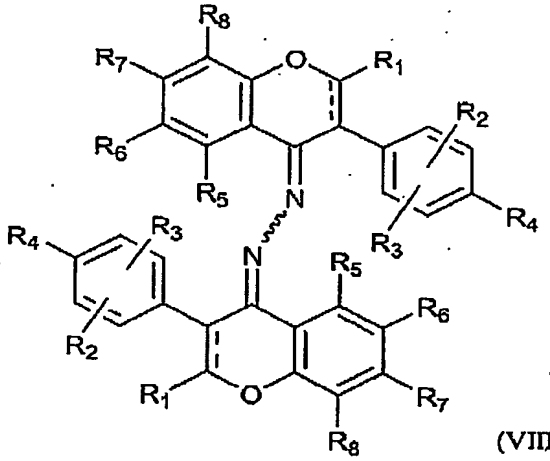
(V)



(VI)



(VII)



(VIII)

wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, $OS(O)R_9$, alkyl, aryl, arylalkyl, thio, alkylthio, bromo, chloro or fluoro,

R_9 is alkyl, fluoroalkyl or arylalkyl,

R_{13}, R_{14} and R_{15} are independently hydrogen, amino, cyano, thio, nitro, or optionally substituted alkyl, haloalkyl, acyl, aryl, arylalkyl or alkylaryl, or the substituents R_{14} and R_{15} together with the nitrogen atom to which they are attached form an optionally substituted cyclic heteroalkyl or heteroaromatic structure,

R_{16} and R_{17} are independently hydrogen, amino, cyano, thio, nitro or optionally substituted alkyl, haloalkyl, acyl, aryl, arylalkyl or alkylaryl, or the substituents R_{16} and R_{17} taken together with the carbon atom to which they are attached form an optionally substituted isoflavonoid ring system, and

the drawing "---" represents either a single bond or a double bond.

3. A compound according to claim 2, wherein

R_1 is hydrogen,

R_2, R_3, R_5, R_6 and R_8 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$, alkyl, aryl or arylalkyl,

R_4 and R_7 are independently hydroxy, OR_9 or $OC(O)R_9$,

R_9 is methyl, ethyl, propyl, isopropyl or trifluoromethyl, and

R_{13}, R_{14} and R_{15} are independently hydrogen, methyl, ethyl, propyl, isopropyl, trifluoromethyl or optionally substituted phenyl, naphthyl or benzyl, or the substituents R_{14} and R_{15} together with the nitrogen atom to which they are attached form an optionally substituted cyclic heteroalkyl or heteroaromatic structure,

R_{16} and R_{17} are independently hydrogen, methyl, ethyl, propyl, isopropyl, trifluoromethyl or optionally substituted phenyl, naphthyl or benzyl, or the substituents R_{16} and R_{17} taken together with the carbon atom to which they are attached form an optionally substituted isoflavonoid ring system, and

the drawing "---" represents either a single bond or a double bond.

4. A compound according to claim 3, wherein

R_1 is hydrogen,

R_2, R_3, R_5, R_6 and R_8 are independently hydrogen, hydroxy, OR_9, $OC(O)R_9$ or methyl,

R_4 and R_7 are independently hydroxy, OR_9 or $OC(O)R_9$,

R_9 is methyl,

R_{13} is hydrogen, methyl, ethyl, trifluoromethyl, phenyl, chlorophenyl, nitrophenyl, toluyl, naphthyl, benzyl, chlorobenzyl, nitrobenzyl or methylbenzyl,

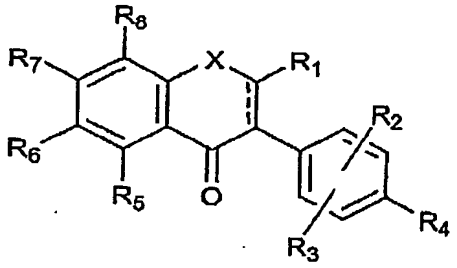
R_{14} is hydrogen and R_{15} is hydrogen, methyl, ethyl, trifluoromethyl, phenyl, chlorophenyl, nitrophenyl, toluyl, naphthyl, benzyl, chlorobenzyl, nitrobenzyl or methylbenzyl, or the substituents R_{14} and R_{15} together with the nitrogen atom to which they are attached form an optionally substituted cyclic heteroalkyl or heteroaromatic structure,

R_{16} and R_{17} are independently hydrogen, methyl, ethyl, trifluoromethyl, phenyl, chlorophenyl, nitrophenyl, toluyl, naphthyl, benzyl, chlorobenzyl, nitrobenzyl or methylbenzyl, or the substituents R_{16} and R_{17} taken together with the carbon atom to which they are attached form an optionally substituted isoflavonoid ring system, and the drawing "---" represents a single bond.

5. A compound according to claim 4 selected from compounds (1) - (14):

4',7-Dihydroxyisoflavanone (phenyl)hydrazone (1)
4',7-Dihydroxyisoflavanone (4-nitrophenyl)hydrazone (2)
4',7-Dihydroxyisoflavanone (4-methylphenyl)hydrazone (3)
4',7-Dihydroxyisoflavanone (benzyl)hydrazone (4)
4',7-Dihydroxyisoflavanone (4',7-dihydroxyisoflavanone)hydrazone (5)
4',7-Dihydroxyisoflavanone (2-chlorophenyl)hydrazone (6)
4',7-Dihydroxyisoflavanone (3-chlorophenyl)hydrazone (7)
4',7-Dihydroxyisoflavanone (4-chlorophenyl)hydrazone (8)
4',7-Dihydroxyisoflavanone (2-pyridyl)hydrazone (9)
4',7-Dihydroxyisoflavanone (4-cyanophenyl)hydrazone (10)
4',7-Dihydroxy-4-methylimino-isoflavan (11)
4',7-Dihydroxyisoflavanone oxime (12)
4-Amino-3',4'-dimethoxy-7-hydroxy-8-methylisoflavan (13)
N-[3',4'-dimethoxy-7-hydroxy-8-methyl-4-chromanyl)-acetamide (14)
which compounds include pharmaceutically acceptable salts thereof.

6. A process for the preparation of a compound of formula (I) as claimed in any one of claims 1 to 5 comprising the step of reacting the 4-keto group of a compound of the formula (X):



(X)

wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and X are as defined in claim 1, and the drawing "---" represents either a single bond or a double bond, with an aminating agent.

7. A method for the treatment, prophylaxis or amelioration of a disease or disorder which method includes the step of administering a therapeutically effective amount of one or more compounds of formula (I) or a pharmaceutically acceptable salt or derivative thereof to a subject,
with the proviso that the compounds and pharmaceutically acceptable salts of
3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-amine
N-(3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-yl)-α-phenyl-benzeneacetamide, and
N-[3,4-Dihydro-3-(4-hydroxyphenyl)-2H-1-benzopyran-4-yl]-α-phenyl-benzeneacetamide
are disclaimed for the treatment, prophylaxis or amelioration of atherosclerosis.

8. A method for the treatment, prevention or amelioration of diseases associated with aberrant cell survival, aberrant cell proliferation, abnormal cellular migration, abnormal angiogenesis, abnormal estrogen/androgen balance, dysfunctional or abnormal steroid genesis, degeneration including degenerative changes within blood vessel walls, inflammation, and immunological imbalance, which comprises administering to a subject one or more compounds of the formula (I) or a pharmaceutically acceptable salt or derivative thereof optionally in association with a carrier and/or excipient,
with the proviso that the compounds and pharmaceutically acceptable salts of
3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-amine
N-(3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-yl)-α-phenyl-benzeneacetamide, and

N-[3,4-Dihydro-3-(4-hydroxyphenyl)-2H-1-benzopyran-4-yl]-α-phenyl-benzeneacetamide are disclaimed for the treatment, prophylaxis or amelioration of atherosclerosis.

9. A method of inducing apoptosis in cells expressing abnormal prosurvival phenotype which comprises contacting said cells with one or more compounds of the formula (I) or a pharmaceutically acceptable salt or derivative thereof optionally in association with a carrier or excipient.

10. A method for inhibiting migration of cells having an abnormal cellular migration phenotype which comprises contacting said cells with a compound of the formula (I) or a pharmaceutically acceptable salt or derivative thereof optionally in association with a carrier or excipient.

11. A method for inhibiting angiogenesis in tissue expressing aberrant angiogenic phenotype which comprises contacting said tissue with a compound of the formula (I) or a pharmaceutically acceptable salt or derivative thereof optionally in association with a carrier or excipient,
with the proviso that the compounds and pharmaceutically acceptable salts of
3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-amine
N-(3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-yl)-α-phenyl-benzeneacetamide, and
N-[3,4-Dihydro-3-(4-hydroxyphenyl)-2H-1-benzopyran-4-yl]-α-phenyl-benzeneacetamide are disclaimed for the treatment, prophylaxis or amelioration of atherosclerosis.

12. A method for the treatment, prevention or amelioration of cancer in a mammal which method comprises the step of bringing a compound of formula (I) or a pharmaceutically acceptable salt or derivative thereof into contact with cancerous tissue in a mammal that is suffering from a tumour, such that neoplastic development in said cancerous tissue is retarded or arrested.

13. Use of one or more compounds of formula (I) or a pharmaceutically acceptable salt or derivative thereof in the manufacture of a medicament for the treatment of a disease or

disorder,
with the proviso that the compounds and pharmaceutically acceptable salts of
3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-amine
N-(3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-yl)-α-phenyl-benzeneacetamide, and
N-[3,4-Dihydro-3-(4-hydroxyphenyl)-2H-1-benzopyran-4-yl]-α-phenyl-benzeneacetamide
are disclaimed for the use in the manufacture of a medicament for the treatment, prophylaxis or amelioration of atherosclerosis.

14. Use of a compound of formula (I) or a pharmaceutically acceptable salt or derivative thereof as an anti-inflammatory agent.

15. An agent for the treatment, prophylaxis or amelioration of a disease or disorder, which agent comprises one or more compounds of formula (I) or a pharmaceutically acceptable salt or derivative thereof,
with the proviso that the compounds and pharmaceutically acceptable salts of
3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-amine
N-(3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-yl)-α-phenyl-benzeneacetamide, and
N-[3,4-Dihydro-3-(4-hydroxyphenyl)-2H-1-benzopyran-4-yl]-α-phenyl-benzeneacetamide
are disclaimed for the treatment, prophylaxis or amelioration of atherosclerosis.

16. A pharmaceutical composition which comprises one or more compounds of formula (I) or a pharmaceutically acceptable salt or derivative thereof in association with one or more pharmaceutical carriers, excipients, auxiliaries and/or diluents,
with the proviso that the compounds and pharmaceutically acceptable salts of
3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-amine
N-(3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-yl)-α-phenyl-benzeneacetamide, and
N-[3,4-Dihydro-3-(4-hydroxyphenyl)-2H-1-benzopyran-4-yl]-α-phenyl-benzeneacetamide
are disclaimed.

17. A drink or food-stuff, which contains one or more compounds of formula (I) or a pharmaceutically acceptable salt or derivative thereof.

18. A compound of formula (I) or a pharmaceutically acceptable salt thereof as herein described with reference to the Examples and/or accompanying drawings.

Y is H or F, and

Z is Cl, Br or CF_3

are specifically excluded, and

with the proviso that the following compounds

3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-amine

N-(3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-yl)-α-phenyl-benzeneacetamide

N-[3,4-Dihydro-3-(4-hydroxyphenyl)-2H-1-benzopyran-4-yl]-α-phenyl-benzeneacetamide

2,3-Dihydro-3-phenyl-4H-1-benzopyran-4-one oxime

2,3-Dihydro-3-phenyl-4H-1-benzopyran-4-one O-acetyloxime

N-[3-(3,4-Dimethoxyphenyl)-3,4-dihydro-7,8-dimethoxy-2H-1-benzopyran-4-yl]-formamide

2,3-Dihydro-2,3-diphenyl-4H-1-benzopyran-4-one hydrazone

4',7-Dimethoxy-isoflavanone oxime

3,4-Dihydro-3-phenyl-2H-1-benzopyran-4-amine

N-(3-Phenyl-4-chromanyl)-acetamide

N-(7-Methoxy-3-phenyl-4-chromanyl)-acetamide

4',7-Dimethoxy-4-isoflavanamine

N-[7-Methoxy-3-(p-methoxyphenyl)-4-chromanyl]-acetamide

7-Methoxy-3-isoflavanamine

2'-Hydroxy-isoflavanone (2,4-dinitrophenyl)hydrazone

7-Methoxy-isoflavanone oxime

7-Methoxy-3',4'-(methylenedioxy)-isoflavanone (2,4-dinitrophenyl)hydrazone

7-Methoxy-isoflavanone phenylhydrazone

5,7-Dimethoxy-isoflavanone (2,4-dinitrophenyl)hydrazone

2,3-Dihydro-3-phenyl-4H-1-benzopyran-4-one oxime

Isoflavanone (2,4-dinitrophenyl)hydrazone

6-Hydroxy-isoflavanone (2,4-dinitrophenyl)hydrazone

7-Hydroxy-isoflavanone (2,4-dinitrophenyl)hydrazone

Isoflavanone semicarbazone

7-Methoxy-3',4'-(methylenedioxy)-isoflavanone (2,4-dinitrophenyl)hydrazone

7-Hydroxy-3',4'-(methylenedioxy)-isoflavanone (2,4-dinitrophenyl)hydrazone